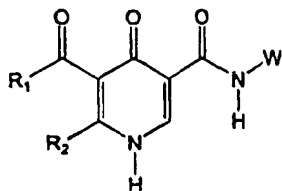




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(54) Title: SUBSTITUTED 1,4-DIHYDRO-4-OXONICOTINIC CARBOXAMIDES: GABA BRAIN RECEPTOR LIGANDS



(a)

## (57) Abstract

Disclosed are compounds of formula (a), or the pharmaceutically acceptable non-toxic salts thereof wherein: R<sub>1</sub> is lower alkyl; R<sub>2</sub> is hydrogen or lower alkyl; or R<sub>1</sub> and R<sub>2</sub> together represent a 2, 3- or 4 carbon alkylene moiety that together with the pyridone ring to which they are attached form a 5, 6 or 7 membered carbocyclic ring; and W is (un)substituted lower alkyl, aryl, arylalkyl, or heteroaryl; or W is NR<sub>3</sub>COR<sub>4</sub>, COR<sub>4</sub>, CONR<sub>3</sub>R<sub>4</sub> or CO<sub>2</sub>R<sub>4</sub> where R<sub>3</sub> and R<sub>4</sub> are the same or different and represent hydrogen or lower alkyl, which compounds are highly selective agonists, antagonists or inverse agonists for GABA<sub>A</sub> brain receptors or prodrugs of agonists, antagonists or inverse agonists for GABA<sub>A</sub> brain receptors. These compounds are useful in the diagnosis and treatment of anxiety, sleep, cognitive and seizure disorders, and overdose with benzodiazepine drugs and for enhancement of alertness.

SUBSTITUTED 1,4-DIHYDRO-4-OXONICOTINIC  
CARBOXAMIDES: GABA BRAIN RECEPTOR LIGANDS

BACKGROUND OF THE INVENTION

5 Field of the Invention

This invention relates to substituted 1,4-dihydro-4-oxonicotinic carboxamides and specifically to such compounds that bind to GABA<sub>A</sub> receptors. This invention also relates to pharmaceutical compositions comprising such compounds. It  
10 further relates to the use of such compounds in treating anxiety, sleep and seizure disorders, and overdoses of benzodiazepine-type drugs, and enhancing alertness.

Description of the Related Art

γ-Aminobutyric acid (GABA) is regarded as one of the major  
15 inhibitory amino acid transmitters in the mammalian brain. Over 40 years have elapsed since its presence in the brain was demonstrated (Roberts & Frankel, J. Biol. Chem. 187: 55-63, 1950; Udenfriend, J. Biol. Chem. 187: 65-69, 1950).— Since that time, an enormous amount of effort has been devoted to  
20 implicating GABA in the etiology of seizure disorders, sleep, anxiety and cognition (Tallman and Gallager, Ann. Rev. Neuroscience 8: 21-44, 1985). Widely, although unequally, distributed through the mammalian brain, GABA is said to be a transmitter at approximately 30% of the synapses in the brain.  
25 GABA mediates many of its actions through a complex of proteins localized both on cell bodies and nerve endings; these are called GABA<sub>A</sub> receptors. Postsynaptic responses to GABA are mediated through alterations in chloride conductance that generally, although not invariably, lead to  
30 hyperpolarization of the cell. Recent investigations have indicated that the complex of proteins associated with postsynaptic GABA responses is a major site of action for a number of structurally unrelated compounds capable of modifying postsynaptic responses to GABA. Drugs that interact  
35 at the GABA<sub>A</sub> receptor can possess a spectrum of

pharmacological activities depending on their abilities to modify the actions of GABA.

1,4-Benzodiazepines, such as diazepam, flurazepam, and triazolam continue to be among the most widely used as  
5 anxiolytics, sedative-hypnotics, muscle relaxants, and anticonvulsants. A number of these compounds are extremely potent drugs; such potency indicates a site of action with a high affinity and specificity for individual receptors. Early electrophysiological studies indicated that a major action of  
10 benzodiazepines was enhancement of GABAergic inhibition. Presently, those compounds possessing activity which enhance the effect of GABA are called agonists, those compounds which decrease the effect of GABA are called inverse agonists, and those compounds which block the effect of GABA are called  
15 antagonists.

The GABA<sub>A</sub> receptor subunits have been cloned from bovine and human cDNA libraries (Schoenfield et al., 1988; Duman et al., 1989). A number of distinct cDNAs were identified as subunits of the GABA<sub>A</sub> receptor complex by cloning and  
20 expression. These are categorized into  $\alpha$ ,  $\beta$ ,  $\gamma$ ,  $\delta$ ,  $\epsilon$ , and provide a molecular basis for the GABA<sub>A</sub> receptor heterogeneity and distinctive regional pharmacology (Shivvers et al., 1980; Levitan et al., 1989). The  $\gamma$  subunit appears to enable drugs like benzodiazepines to modify the GABA responses (Pritchett  
25 et al., 1989). The presence of low Hill coefficients in the binding of ligands to the GABA<sub>A</sub> receptor indicates unique profiles of subtype specific pharmacological action.

With the discovery of the "receptor" for the benzodiazepines and the subsequent definition of the nature of  
30 the interaction between GABA and the benzodiazepines, it appears that the behaviorally important interactions of the benzodiazepines with different neurotransmitter systems are due in a large part to the enhanced ability of GABA itself to modify these systems. Each modified system, in turn, may be

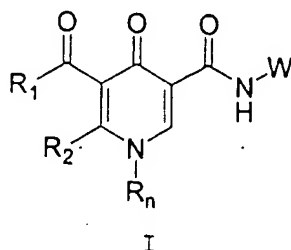
associated with the expression of a behavior. Depending on the mode of interaction, these compounds are capable of producing a spectrum of activities (either sedative, anxiolytic, and anticonvulsant, or wakefulness, seizures, and anxiety).

5

SUMMARY OF THE INVENTION

This invention provides novel compounds of Formula I which interact with a GABA<sub>A</sub> binding site, the benzodiazepine receptor.

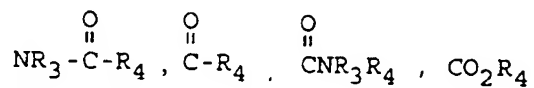
5 The invention provides compounds useful in the diagnosis and treatment of anxiety, sleep, and seizure disorders, overdose with benzodiazepine drugs and for enhancement of memory. The invention also provides pharmaceutical compositions comprising compounds of Formula I. Accordingly,  
 10 a broad embodiment of the invention is directed to compounds of Formula I:



wherein:

- 15  $R_n$  = hydrogen or  $C_1$ - $C_6$  alkyl;  
 $R_1$  is lower alkyl;  
 $R_2$  is hydrogen or lower alkyl; or  
 $R_1$  and  $R_2$  together represent a 2, 3, or 4 carbon alkylene  
 moiety that together with the pyridone ring to which they  
 20 are attached form a 5, 6, or 7 membered oxo-substituted  
 carbocyclic ring where each carbon atom of said alkylene  
 moiety is optionally substituted with halogen, hydroxy,  
 $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkoxy, amino, mono- or di( $C_1$ -  
 $C_6$ )alkylamino, or trifluoromethyl; and  
 25  $W$  is lower alkyl optionally substituted with one or two groups  
 selected from halogen, hydroxy, lower alkoxy, amino, or  
 mono- or dialkyl amino where each alkyl portion is  
 independently lower alkyl; or  
 $W$  is aryl, arylalkyl, or heteroaryl, where the ring portion of  
 30 each is optionally substituted with one or two groups

independently selected from halogen, trifluoromethyl, cyano, hydroxy, lower alkyl, lower alkoxy, amino, mono or dialkylamino where each alkyl portion is lower alkyl, alkylaminoalkyl where each alkyl portion is lower alkyl, or



where R<sub>3</sub> and R<sub>4</sub> are the same or different and represent hydrogen or lower alkyl.

These compounds are highly selective agonists, antagonists or inverse agonists for GABA<sub>A</sub> brain receptors or prodrugs of agonists, antagonists or inverse agonists for GABA<sub>A</sub> brain receptors. These compounds are therefore useful in the diagnosis and treatment of anxiety, sleep and seizure disorders, overdose with benzodiazepine drugs and for enhancement of memory.

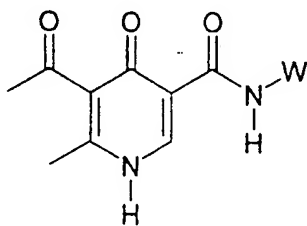
### DETAILED DESCRIPTION OF THE INVENTION

The novel compounds encompassed by the instant invention can be described by general Formula I set forth above or the pharmaceutically acceptable non-toxic salts thereof.

5 Preferred compounds of Formula I are those where  $R_n$  is hydrogen. Other preferred compounds of Formula I are those where W is mono- or disubstituted phenyl or benzyl. Preferred phenyl and benzyl substituents include halogen, preferably fluoro, chloro and bromo,  $C_1$ - $C_2$  alkyl,  $C_1$ - $C_6$  alkylamino( $C_1$ - $C_6$ )alkyl, more preferably methylamino( $C_1$ - $C_2$ )alkyl groups, and  
10  $C_1$ - $C_2$  alkoxy.

Other preferred compounds of Formula I are those where W is thiazolyl or pyridyl substituted with one or two groups selected from  $C_1$ - $C_6$  alkoxy, halogen, preferably chloro and  
15 fluoro, and 1- or 2-methylaminoethyl.

The present invention also encompasses compounds of Formula II



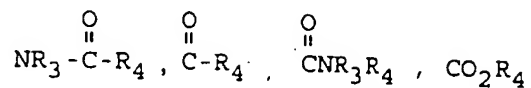
II

20 wherein:

W is lower alkyl optionally substituted with one or two groups selected from halogen, hydroxy, lower alkoxy, amino, or mono- or dialkyl amino where each alkyl portion is independently lower alkyl; or

25 W is aryl, arylalkyl, or heteroaryl, where the ring portion of each is optionally substituted with one or two groups independently selected from halogen, trifluoromethyl, cyano, hydroxy, lower alkyl, lower alkoxy, amino, mono or dialkylamino where each alkyl portion is lower alkyl,

methylaminoalkyl where each alkyl portion is lower alkyl,  
or



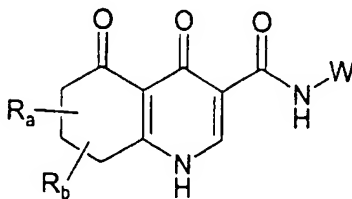
where R<sub>3</sub> and R<sub>4</sub> are the same or different and represent  
hydrogen or lower alkyl.

More preferred compounds of Formula II are where W is  
lower alkyl or aryl, arylakyl, or heteroaryl, where each aryl  
is optionally substituted with one or two groups independently  
selected from halogen, lower alkyl, lower alkoxy, or  
methylaminoalkyl where each alkyl portion is lower alkyl.

Even more preferred compounds of Formula II are where W  
is aryl optionally substituted with one or two groups  
independently selected from fluorine, methyl, methoxy, or  
ethoxy.

Other preferred compounds of Formula II are those where W  
is C<sub>1</sub>-C<sub>6</sub> alkyl, optionally substituted with halogen, amino, or  
mono- or di(C<sub>1</sub>-C<sub>6</sub>) alkyl amino.

In addition, the present invention encompasses compounds  
of Formula III, i.e., compounds where R<sub>1</sub> and R<sub>2</sub> together  
represent a 3-carbon alkylene moiety that together with the  
pyridone ring to which they are attached form a 6-membered oxo-  
substituted carbocyclic ring:



III

wherein:

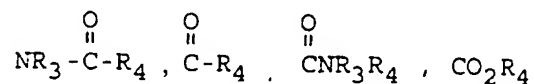
R<sub>a</sub> is hydrogen, halogen, hydroxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy,  
amino, mono- or di(C<sub>1</sub>-C<sub>6</sub>)alkylamino, or trifluoromethyl;



$R_b$  is hydrogen, halogen, hydroxy,  $C_1-C_6$  alkyl,  $C_1-C_6$  alkoxy, amino, mono- or di( $C_1-C_6$ )alkylamino, or trifluoromethyl;

W is lower alkyl optionally substituted with one or two groups selected from halogen, hydroxy, lower alkoxy, amino, or  
 5 mono- or dialkyl amino where each alkyl portion is independently lower alkyl; or

W is aryl, arylalkyl, or heteroaryl, where the ring portion of each is optionally substituted with one or two groups independently selected from halogen, trifluoromethyl,  
 10 cyano, hydroxy, lower alkyl, lower alkoxy, amino, mono or dialkylamino where each alkyl portion is lower alkyl, or methylaminoalkyl where each alkyl portion is lower alkyl; or



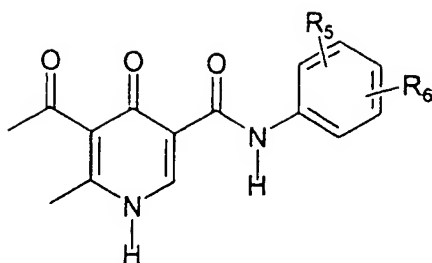
15 where  $R_3$  and  $R_4$  are the same or different and represent hydrogen or lower alkyl.

Preferred compounds of the invention are those of Formula III where  $R_a$  and  $R_b$  are independently hydrogen  $C_1-C_6$  alkyl, or  
 20 halogen. More preferably, only one of  $R_a$  and  $R_b$  maybe a non-hydrogen group selected from  $C_1-C_6$  alkyl or halogen, preferably chloro or fluoro. Still other preferred compounds of Formula III are those where  $R_a$  is methyl or, more preferably, hydrogen.

Other more preferred compounds of Formula III are where W  
 25 is alkyl or aryl, arylakyl, or heteroaryl, where each aryl is optionally substituted with one or two groups independently selected from halogen, lower alkyl, lower alkoxy, or methylaminoalkyl where each alkyl portion is lower alkyl.

Even more preferred compounds of Formula III are where W  
 30 is aryl optionally substituted independently with fluorine or methoxy.

A preferred group of compounds of the invention is encompassed by formula IV:



IV

wherein:

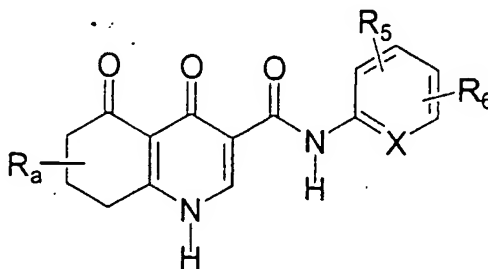
5 R<sub>5</sub> and R<sub>6</sub> are the same or different and represent hydrogen, halogen, hydroxy, lower alkyl, lower alkoxy, amino, mono or dialkylamino where each alkyl portion is lower alkyl, or methylaminoalkyl where each alkyl portion is lower alkyl.

10 More preferred compounds of Formula IV are where R<sub>5</sub> and R<sub>6</sub> are the same or different and represent hydrogen, halogen, lower alkyl, or lower alkoxy.

Even more preferred compounds of Formula IV are where R<sub>5</sub> and R<sub>6</sub> together represent 2,4-difluoro, 2,6-difluoro, 2-  
15 fluoro-4-methoxy, 4-methoxy, 2-fluoro, 4-ethoxy, 3-fluoro, 3-methyl, and 2-methoxy.

Particularly, preferred compounds of Formula IV are those where R<sub>5</sub> is hydrogen and R<sub>6</sub> is 2-fluoro.

20 Other preferred compounds of the invention are represented by Formula V.



V

wherein:

R<sub>a</sub> is hydrogen, halogen, hydroxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, amino, mono- or di(C<sub>1</sub>-C<sub>6</sub>)alkylamino, or trifluoromethyl;

X is carbon or nitrogen; and

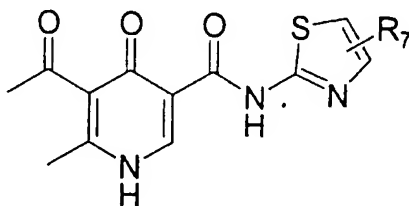
R<sub>5</sub> and R<sub>6</sub> are the same or different and represent hydrogen,  
5 halogen, hydroxy, lower alkyl, lower alkoxy, amino, mono or dialkylamino where each alkyl portion is lower alkyl, or methylaminoalkyl where each alkyl portion is lower alkyl.

10 More preferred compounds of Formula V are where X is carbon and R<sub>5</sub> and R<sub>6</sub> are the same or different and represent hydrogen, halogen, lower alkyl, or lower alkoxy.

Even more preferred compounds of Formula V are where X is carbon and R<sub>5</sub> is hydrogen and R<sub>6</sub> is hydrogen or 2-fluoro.

15 Particularly preferred compounds of Formula V are where R<sub>5</sub> is hydrogen and R<sub>6</sub> is 2-fluoro.

Still other preferred compounds of the invention are those of Formula VI.



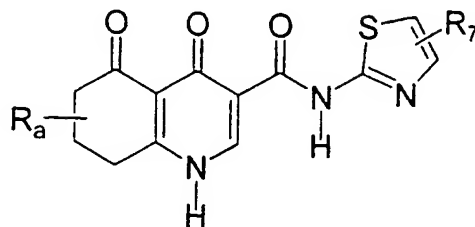
VI

wherein:

R<sub>7</sub> is hydrogen, halogen, hydroxy, lower alkyl, lower alkoxy, amino, mono or dialkylamino where each alkyl portion is  
25 lower alkyl, or methylaminoalkyl where each alkyl portion is lower alkyl.

More preferred compounds of Formula VI are where R<sub>7</sub> is hydrogen, halogen, or lower alkyl.

Even more preferred compounds of Formula VI are where R<sub>7</sub> is 4-C1-C3 alkyl, preferably methyl.



VII

wherein:

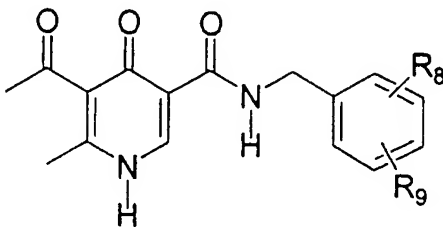
R<sub>a</sub> is hydrogen, halogen, hydroxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, amino, mono- or di(C<sub>1</sub>-C<sub>6</sub>)alkylamino, or trifluoromethyl;

R<sub>7</sub> is hydrogen, halogen, hydroxy, lower alkyl, lower alkoxy, amino, mono or dialkylamino where each alkyl portion is lower alkyl, or methylaminoalkyl where each alkyl portion is lower alkyl.

More preferred compounds of Formula VII are where R<sub>7</sub> is hydrogen, halogen, or lower alkyl.

An even more preferred compound of Formula VII is where R<sub>7</sub> is hydrogen.

Another group of preferred compounds is encompassed by Formula VIII:



VIII

wherein:

R<sub>8</sub> and R<sub>9</sub> are the same or different and represent hydrogen, halogen, cyano, hydroxy, lower alkyl, lower alkoxy,

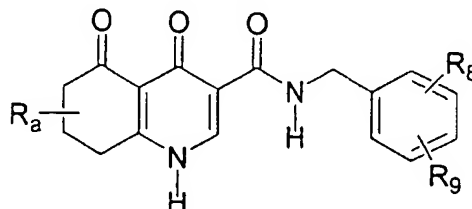
amino, mono or dialkylamino where each alkyl portion is lower alkyl, methylaminoalkyl where each alkyl portion is lower alkyl.

5 More preferred compounds of Formula VIII are where  $R_8$  and  $R_9$  are the same or different and represent hydrogen, halogen, lower alkyl, or lower alkoxy.

Even more preferred compounds of Formula VIII are where  $R_8$  and  $R_9$  together represent 2,3-difluoro or  $R_8$  is hydrogen and  $R_9$  is 2-fluoro, 4-chloro, or 4-(1-methylaminoethyl).

Highly preferred compounds of Formula VIII are those where  $R_8$  is hydrogen and  $R_9$  is 2-fluoro.

15 Still another group of preferred compounds of the invention are represented by Formula IX:



IX

wherein:

$R_a$  is hydrogen, halogen, hydroxy,  $C_1$ - $C_6$  alkyl,  $C_1$ - $C_6$  alkoxy, amino, mono- or di( $C_1$ - $C_6$ )alkylamino, or trifluoromethyl;

20  $R_8$  and  $R_9$  are the same or different and represent hydrogen, halogen, cyano, hydroxy, lower alkyl, lower alkoxy, amino, mono or dialkylamino where each alkyl portion is lower alkyl, methylaminoalkyl where each alkyl portion is lower alkyl.

25 More preferred compounds of Formula IX are where  $R_8$  and  $R_9$  are the same or different and represent hydrogen, halogen, lower alkyl, or lower alkoxy.

Even more preferred compounds of Formula IX are where R<sub>8</sub> and R<sub>9</sub> are hydrogen or R<sub>8</sub> is hydrogen and R<sub>9</sub> is 4-methoxy or 2-fluoro.

Highly preferred compounds of Formula IX are where R<sub>8</sub> is  
5 hydrogen and R<sub>9</sub> is 2-fluoro.

By "alkyl", "lower alkyl", and "C<sub>1</sub>-C<sub>6</sub> alkyl" in the present invention is meant straight or branched chain alkyl groups having 1-6 carbon atoms, such as, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, pentyl, 2-  
10 pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl, and 3-methylpentyl.

By "alkoxy", "lower alkoxy", and "C<sub>1</sub>-C<sub>6</sub> alkoxy" in the present invention is meant straight or branched chain alkoxy groups having 1-6 carbon atoms, such as, for example, methoxy,  
15 ethoxy, propoxy, isopropoxy, n-butoxy, sec-butoxy, tert-butoxy, pentoxy, 2-pentoxy, isopentoxy, neopentoxy, hexoxy, 2-hexoxy, 3-hexoxy, and 3-methylpentoxy.

By the term "halogen" in the present invention is meant fluorine, bromine, chlorine, and iodine.

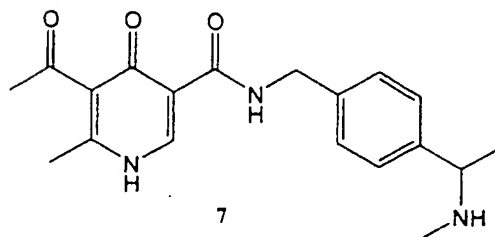
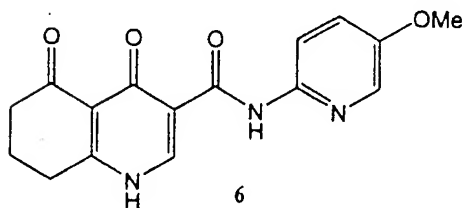
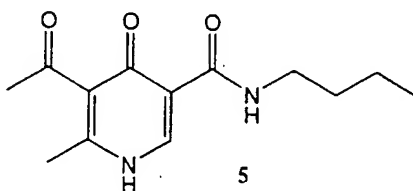
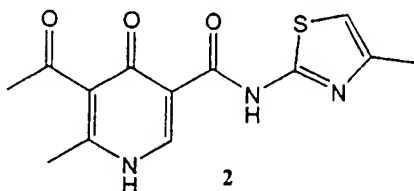
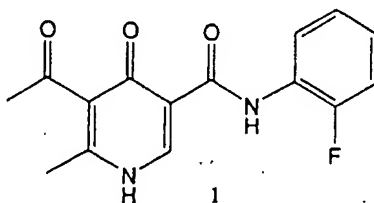
By heteroaryl is meant one or more aromatic ring systems  
20 of 5-, 6-, or 7-membered rings containing at least one and up to four heteroatoms selected from nitrogen, oxygen, or sulfur. Such heteroaryl groups include, for example, thienyl, furanyl, thiazolyl, imidazolyl, (is)oxazolyl, pyridyl, pyrimidinyl,  
25 (iso)quinolinyl, naphthyridinyl, benzimidazolyl, benzoxazolyl. Preferred heteroaryls are thiazolyl and pyridyl groups that are optionally substituted as described herein.

By aryl is meant an aromatic carbocyclic group having a single ring (e.g., phenyl), multiple rings (e.g., biphenyl),  
30 or multiple condensed rings in which at least one is aromatic, (e.g., 1,2,3,4-tetrahydronaphthyl, naphthyl, anthryl, or phenanthryl), which is optionally mono-, di-, or trisubstituted with, e.g., halogen, lower alkyl, lower alkoxy,

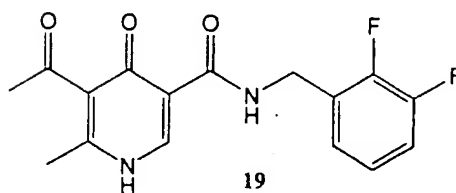
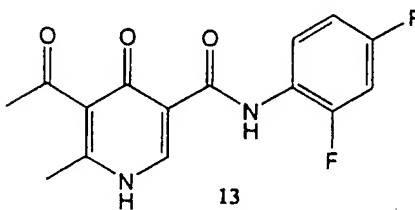
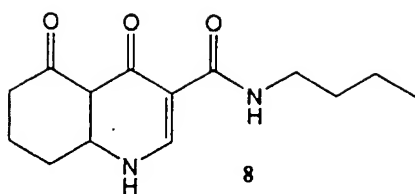
lower alkylthio, trifluoromethyl, lower acyloxy, aryl, heteroaryl, and hydroxy. A preferred aryl group is phenyl that is optionally substituted as described herein.

Representative compounds of the invention are shown below  
5 in Table 1.

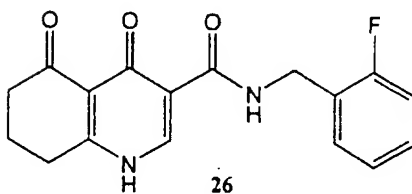
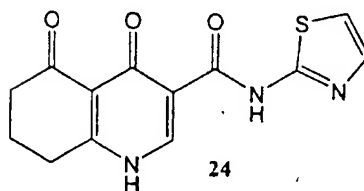
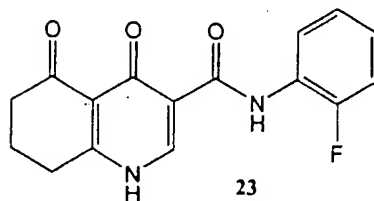
Table 1



10



5



10

Representative compounds of the present invention, which are encompassed by Formula I, include, but are not limited to



the compounds in Table I and their pharmaceutically acceptable acid or base addition salts. In addition, if the compound of the invention is obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid salt.

5 Conversely, if the product is a free base, an addition salt, particularly a pharmaceutically acceptable addition salt, may be produced by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts

10 from base compounds.

Non-toxic pharmaceutically acceptable salts include salts of acids such as hydrochloric, phosphoric, hydrobromic, sulfuric, sulfinic, formic, toluenesulfonic, methanesulfonic, nitric, benzoic, citric, tartaric, maleic, hydroiodic,

15 alkanolic such as acetic,  $\text{HOOC}-(\text{CH}_2)_n-\text{COOH}$  where  $n$  is 0-4, and the like. Those skilled in the art will recognize a wide variety of non-toxic pharmaceutically acceptable addition salts.

The present invention also encompasses the acylated

20 prodrugs of the compounds of Formula I. Those skilled in the art will recognize various synthetic methodologies which may be employed to prepare non-toxic pharmaceutically acceptable addition salts and acylated prodrugs of the compounds encompassed by Formula I.

25 The compounds of Formula I and their salts are suitable for the diagnosis and treatment of anxiety, Down Syndrome, sleep, cognitive and seizure disorders, and overdose with benzodiazepine drugs and for enhancement of alertness, both in human and non-human animals and domestic pets, especially dogs

30 and cats and farm animals such as sheep, swine and cattle.

The compounds of general Formula I may be administered orally, topically, parenterally, by inhalation or spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and

vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition, there is provided a pharmaceutical formulation comprising a compound of general Formula I and a pharmaceutically acceptable carrier. One or more compounds of general Formula I may be present in association with one or more non-toxic pharmaceutically acceptable carriers and/or diluents and/or adjuvants and if desired other active ingredients. The pharmaceutical compositions containing compounds of general Formula I may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs.

Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period.

For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with  
5 an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

Aqueous suspensions contain the active materials in  
10 admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydropropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia;  
15 dispersing or wetting agents may be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example  
20 heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example  
25 polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

30 Oily suspensions may be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl

alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide palatable oral preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

5        Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents  
10 are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

      Pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be  
15 a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or  
20 partial esters derived from fatty acids and hexitol, anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

25        Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile  
30 injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be sterile injectable solution or

suspension in a non-toxic parentally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride  
5 solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

10 The compounds of general Formula I may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid  
15 at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

Compounds of general Formula I may be administered parenterally in a sterile medium. The drug, depending on the  
20 vehicle and concentration used, can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as local anesthetics, preservatives and buffering agents can be dissolved in the vehicle.

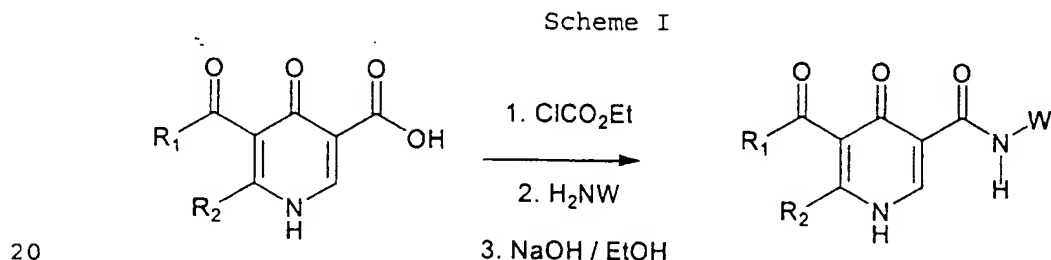
Dosage levels of the order of from about 0.1 mg to about  
25 140 mg per kilogram of body weight per day are useful in the treatment of the above-indicated conditions (about 0.5 mg to about 7 g per patient per day). The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host  
30 treated and the particular mode of administration. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of

factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

For administration to non-human animals, the composition may also be added to the animal feed or drinking water. It will be convenient to formulate these animal feed and drinking water compositions with a mullet-dose of the drug so that the animal takes in an appropriate quantity of the composition along with its diet. It will also be convenient to present the composition as a premix for addition to the feed or drinking water.

An illustration of the preparation of compounds of the present invention is shown in Scheme I. The appropriate pyridin-4-one-3-carboxylic acid is prepared essentially according to the procedures described in *J. Het. Chem.* 1975, 1245.



Where  $R_1$ ,  $R_2$  and  $W$  are as defined above for Formula I.

Those having skill in the art will recognize that the starting materials may be varied and additional steps employed to produce compounds encompassed by the present invention, as demonstrated by the following examples.

As shown in Scheme I, a carboxylic acid is treated with an acid chloride, such as, for example, ethyl chloroformate, in the presence of a base like triethylamine. The resulting mixed anhydride is subsequently treated with an amine to afford the desired amide. N-alkylated compounds, i.e., where

$R_n$  is  $C_1-C_6$  alkyl, can be prepared by protecting the acid group prior to coupling with the amine  $WNH_2$ , or after coupling without any protecting groups depending on the substituents on the various groups  $R_1$ ,  $R_2$ , and  $W$ .

5 The disclosures in this application of all articles and references, including patents, are incorporated herein by reference.

The invention is illustrated further by the following examples which are not to be construed as limiting the  
10 invention in scope or spirit to the specific procedures described in them.

The starting materials and various intermediates may be obtained from commercial sources, prepared from commercially available organic compounds, or prepared using well known  
15 synthetic methods.

Representative examples of methods for preparing intermediates of the invention are set forth below.

#### Example 1

20 N-(2(4-Methylthiazolyl))-1,4-dihydro-4-oxo-5-acetyl-6-methyl  
nicotinic-3-carboxamide (Compound 2)

A quantity of 150 mg (0.768 mmole, 1.0 eq) of 1,4-dihydro-4-oxo-5-acetyl-6-methyl-3-carboxylic acid is dissolved in 5 ml THF and 1 ml DMF and treated at 0° C with 0.16 ml (1.69  
25 mmole, 2.2 eq) TEA followed by 0.24 ml (1.69 mmole, 2.2 eq) of ethyl chloroformate. The resulting solution is stirred for 30 min. at which time 150 mg (1.69 mmole, 2.2 eq) of 4-methyl-2-amino-thiazole is added. The solution is allowed to warm to room temperature for 1 hr before the addition of 20 ml of  $H_2O$ .  
30 The THF is removed under reduced pressure, and the resulting solid is filtered and washed with  $H_2O$  and then  $Et_2O$ . The solid is then slurried in 1 ml  $EtOH$ /5 ml 10%  $NaOH$  and warmed to 90° C for 10 min., cooled to 0° C, and the pH adjusted to 9.0 with 3N  $HCl$ . The crude product is filtered, washed with  $H_2O$  and then

Et<sub>2</sub>O, and purified by chromatography (silica gel, 10% CH<sub>3</sub>OH/50% EtOAc/40% hexanes) to yield 44 mg of N-(2(4-Methylthiazolyl))-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide (Compound 2), mp 237-238° C.

5

#### Example 2

##### N-(Butyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide (Compound 5)

A quantity of 150 mg (0.768 mmole, 1.0 eq) of 1,4-dihydro-4-oxo-5-acetyl-6-methyl-3-carboxylic acid is dissolved in 5 ml THF and 1 ml DMF and treated at 0° C with 0.16 ml (1.69 mmole, 2.2 eq) TEA followed by 0.24 ml (1.69 mmole, 2.2 eq) of ethyl chloroformate. The resulting solution is stirred for 30 min at which time 0.18 ml (1.69 mmole, 2.2 eq) of n-Butyl amine is added. The solution is allowed to warm to room temperature for 1 hr before the addition of 20 ml of H<sub>2</sub>O. The THF is removed under reduced pressure, the resulting solid is filtered and washed with H<sub>2</sub>O and then Et<sub>2</sub>O, and purified by chromatography (silica gel, 10% CH<sub>3</sub>OH/50% EtOAc/40% hexanes) to yield 40 mg of N-(Butyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide (Compound 5), mp 119-120° C.

#### Example 3

The following compounds are prepared essentially according to the procedures set forth in Examples 1 and 2:

(a) N-(2-Fluorophenyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide; mp 261-262°C (Compound 1).

(b) N-(4-Methoxyphenyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide; mp 194-196°C (Compound 3).

(c) N-(Phenyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide; mp 217-218°C (Compound 4).



- (d) N-(4-Methoxy-2-pyridyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide; mp 235-237°C (Compound 6).
- 5 (e) N-(4-(±)-(1-Methylaminoethyl)benzyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide; mp 120-123°C (Compound 7).
- (f) N-(n-Butyl)-1,4,5,6,7,8-hexahydroquinoline-4,5-  
10 dione-nicotinic-3-carboxamide; mp 35-37°C (Compound 8).
- (g) N-(4-Ethoxyphenyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide; mp 179-180°C (Compound 9).
- 15 (h) N-(3-Fluorophenyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide; mp 235-237°C (Compound 10).
- (i) N-(2-Fluoro-4-methoxyphenyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide; mp 240-242°C (Compound  
20 11).
- (j) N-(3-Tolyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide; mp 198-200°C (Compound 12).
- 25 (k) N-(2,4-Difluorophenyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide; mp 278-280°C (Compound 13).
- (l) N-(2,6-Difluorophenyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide; mp 107-108°C (Compound 14).  
30
- (m) N-(Benzyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide; mp 198-200°C (Compound 15).

- (n) N-(2-Methoxyphenyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide; mp 208-210°C (Compound 16).
- (o) N-(3-(Methylaminomethyl)phenyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide; mp 180-185°C (Compound 17).
- (p) N-(2-Fluorobenzyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide; mp 185-187°C (Compound 18).
- (q) N-(2,3-Difluorobenzyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide; mp 249-250°C (Compound 19).
- (r) N-(Isoamyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide; mp 165-167°C (Compound 20).
- (s) N-(4-Chlorobenzyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide; mp 54-55°C (Compound 21).
- (t) N-(Phenyl)-1,4,5,6,7,8-hexahydroquinoline-4,5-dione-nicotinic-3-carboxamide; mp 310-312°C (Compound 22).
- (u) N-(2-Fluorophenyl)-1,4,5,6,7,8-hexahydroquinoline-4,5-dione-nicotinic-3-carboxamide; mp 280-282°C (Compound 23).
- (v) N-(2-Thiazolyl)-1,4,5,6,7,8-hexahydroquinoline-4,5-dione-nicotinic-3-carboxamide; mp 284-285°C (Compound 24).
- (w) N-(Benzyl)-1,4,5,6,7,8-hexahydroquinoline-4,5-dione-nicotinic-3-carboxamide; mp 295-297°C (Compound 25).
- (x) N-(2-Fluorobenzyl)-1,4,5,6,7,8-hexahydroquinoline-4,5-dione-nicotinic-3-carboxamide; mp 291-292°C (Compound 26).

(y) N-(4-Methoxybenzyl)-1,4,5,6,7,8-hexahydroquinoline-4,5-dione-nicotinic-3-carboxamide; mp 265-267°C (Compound 27).

5 (z) N-(2-(4-methoxy)pyridyl)-1,4,5,6,7,8-hexahydroquinoline-4,5-dione-nicotinic-3-carboxamide; mp 235-237°C (Compound 28).

(aa) N-(2-thiazolyl)-1,4,5,6,7,8-hexahydroquinoline-4,5-dione-nicotinic-3-carboxamide; mp 292-294°C (Compound 29).

#### EXAMPLE 4

The pharmaceutical utility of compounds of this invention are indicated by the following assay for GABA<sub>A</sub> receptor  
15 binding activity.

Assays are carried out as described in Thomas and Tallman (*J. Bio. Chem.* 156: 9838-9842, *J. Neurosci.* 3: 433-440, 1983). Rat cortical tissue is dissected and homogenized in 25 volumes (w/v) of 0.05 M Tris HCl buffer (pH 7.4 at 4 °C). The  
20 tissue homogenate is centrifuged in the cold (4°) at 20,000 x g for 20'. The supernatant is decanted and the pellet is rehomogenized in the same volume of buffer and again centrifuged at 20,000 x g. The supernatant is decanted and the pellet is frozen at -20°C overnight. The pellet is then  
25 thawed and rehomogenized in 25 volume (original wt/vol) of buffer and the procedure is carried out twice. The pellet is finally resuspended in 50 volumes (w/vol) of 0.05 M Tris HCl buffer (pH 7.4 at 40°C).

Incubations contain 100 ml of tissue homogenate, 100 ml  
30 of radioligand 0.5 nM (<sup>3</sup>H-RO15-1788 [<sup>3</sup>H-Flumazenil] specific activity 80 Ci/mmol), drug or blocker and buffer to a total volume of 500 ml. Incubations are carried for 30 min at 4°C then are rapidly filtered through GFB filters to separate free

and bound ligand. Filters are washed twice with fresh 0.05 M Tris HCl buffer (pH 7.4 at 4°C) and counted in a liquid scintillation counter. 1.0 mM diazepam is added to some tubes to determine nonspecific binding. Data are collected in triplicate determinations, averaged and % inhibition of total specific binding is calculated. Total Specific Binding = Total - Nonspecific. In some cases, the amounts of unlabeled drugs is varied and total displacement curves of binding are carried out. Data are converted to IC<sub>50</sub> or K<sub>i</sub>. The K<sub>i</sub>'s of the compounds described herein are generally less than 1 μM.

#### EXAMPLE 5

In addition, the following assay may be used to determine if the compounds of the invention are agonists, antagonists, or inverse agonists, and, therefore, their specific pharmaceutical utility. The following assay can be employed to determine specific GABA<sub>A</sub> receptor activity.

Assays are carried out as described in White and Gurley (NeuroReport 6: 1313-1316, 1995) and White, Gurley, Hartnett, Stirling, and Gregory (Receptors and Channels 3: 1-5, 1995) with modifications. *Xenopus Laevis* oocytes are enzymatically isolated and injected with non-polyadenylated cRNA mixed in a ratio of 4:1:4 for human derived α, β, and γ subunits, respectively. For each subunit combination, sufficient message is injected to result in current amplitudes of >10 nA when 1 μM GABA is applied.

Electrophysiological recordings are carried out using the two electrode voltage-clamp technique at a membrane holding potential of -70 mV.

Compounds are evaluated against a GABA concentration that evokes <10% of the maximal evokable GABA current. Each oocyte is exposed to increasing concentrations of compound in order to evaluate a concentration/effect relationship. Compound efficacy is expressed as a percent-change in current

amplitude:  $100 * ((I_c/I) - 1)$ , where  $I_c$  is the GABA evoked current amplitude observed in the presence of compound and  $I$  is the GABA evoked current amplitude observed in the absence of compound.

5        Specificity of a compound for the Ro15-1788 site is determined following completion of the concentration/effect curve. After washing the oocyte sufficiently to remove previously applied compound, the oocyte is exposed to GABA + 1  $\mu$ M Ro15-1788, followed by exposure to GABA + 1  $\mu$ M Ro15-1788 +  
10        compound. Percent change due to addition of compound is calculated as described above. Any percent change observed in the presence of Ro15-1788 is subtracted from the percent changes in current amplitude observed in the absence of 1  $\mu$ M Ro15-1788. These net values are used for the calculation of  
15        average efficacy and  $EC_{50}$  values.

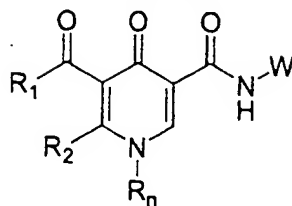
To evaluate average efficacy and  $EC_{50}$  values, the concentration/effect data are averaged across cells and fit to the logistic equation. Average values are reported as mean  $\pm$  standard error.

20

The invention and the manner and process of making and using it, are now described in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, to make and use the same. It is to be  
25        understood that the foregoing describes preferred embodiments of the present invention and that modifications may be made therein without departing from the spirit or scope of the present invention as set forth in the claims. To particularly point out and distinctly claim the subject matter regarded as  
30        invention, the following claims conclude this specification.

## WHAT IS CLAIMED IS:

1. A compound of the formula:



or the pharmaceutically acceptable non-toxic salts thereof

5 wherein:

R<sub>1</sub> is lower alkyl;

R<sub>2</sub> is hydrogen or lower alkyl; or

R<sub>1</sub> and R<sub>2</sub> together represent a 2, 3, or 4 carbon alkylene moiety that together with the pyridone ring to which they are attached form a 5, 6, or 7 membered oxo-substituted carbocyclic ring where each carbon atom of said alkylene moiety is optionally substituted with hydroxy, halogen, C1-C6 alkyl, amino, C1-C6 alkoxy, or trifluoromethyl; and

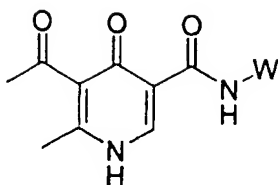
10 W is lower alkyl optionally substituted with one or two groups selected from halogen, hydroxy, lower alkoxy, amino, or mono- or dialkyl amino where each alkyl portion is independently lower alkyl; or

15 W is aryl, arylalkyl, or heteroaryl, where the ring portion of each is optionally substituted with one or two groups independently selected from halogen, trifluoromethyl, cyano, hydroxy, lower alkyl, lower alkoxy, amino, mono- or dialkylamino where each alkyl portion is lower alkyl, methylaminoalkyl where each alkyl portion is lower alkyl, or

20 
$$\text{NR}_3-\overset{\overset{\text{O}}{\parallel}}{\text{C}}-\text{R}_4, \overset{\overset{\text{O}}{\parallel}}{\text{C}}-\text{R}_4, \overset{\overset{\text{O}}{\parallel}}{\text{C}}\text{NR}_3\text{R}_4, \text{CO}_2\text{R}_4$$

where R<sub>3</sub> and R<sub>4</sub> are the same or different and represent hydrogen or lower alkyl.

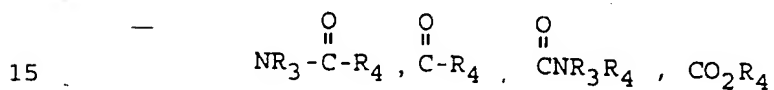
2. A compound according to claim 1 of the formula:



or the pharmaceutically acceptable non-toxic salts thereof  
wherein:

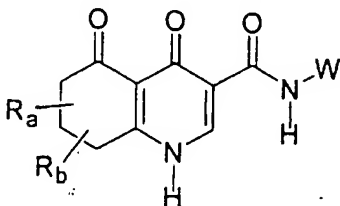
W is lower alkyl optionally substituted with one or two groups  
5 selected from halogen, hydroxy, lower alkoxy, amino, or  
mono- or dialkyl amino where each alkyl portion is  
independently lower alkyl; or

W is aryl, arylalkyl, or heteroaryl, where the ring portion of  
each is optionally substituted with one or two groups  
10 independently selected from halogen, trifluoromethyl,  
cyano, hydroxy, lower alkyl, lower alkoxy, amino, mono or  
dialkylamino where each alkyl portion is lower alkyl,  
methylaminoalkyl where each alkyl portion is lower alkyl,  
or



where  $\text{R}_3$  and  $\text{R}_4$  are the same or different and represent  
hydrogen or lower alkyl.

3. A compound according to claim 1 of the formula:



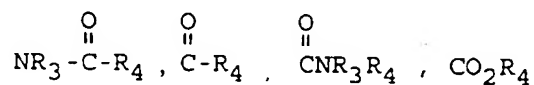
20 or the pharmaceutically acceptable non-toxic salts thereof  
wherein:

$\text{R}_a$  is hydrogen, halogen, hydroxy,  $\text{C}_1\text{-C}_6$  alkyl,  $\text{C}_1\text{-C}_6$  alkoxy,  
amino, mono- or di( $\text{C}_1\text{-C}_6$ )alkylamino, or trifluoromethyl;

25  $\text{R}_b$  is halogen, hydroxy,  $\text{C}_1\text{-C}_6$  alkyl,  $\text{C}_1\text{-C}_6$  alkoxy, amino, mono-  
or di( $\text{C}_1\text{-C}_6$ )alkylamino, or trifluoromethyl;

W is lower alkyl optionally substituted with one or two groups selected from halogen, hydroxy, lower alkoxy, amino, or mono- or dialkyl amino where each alkyl portion is independently lower alkyl; or

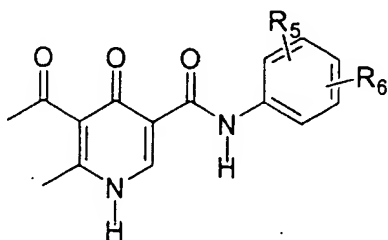
- 5 W is aryl, arylalkyl, or heteroaryl, where the ring portion of each is optionally substituted with one or two groups independently selected from halogen, trifluoromethyl, cyano, hydroxy, lower alkyl, lower alkoxy, amino, mono- or dialkylamino where each alkyl portion is lower alkyl, methylaminoalkyl where each alkyl portion is lower alkyl,  
 10 or



where R<sub>3</sub> and R<sub>4</sub> are the same or different and represent hydrogen or lower alkyl.

15

4. A compound according to claim 1 of the formula:



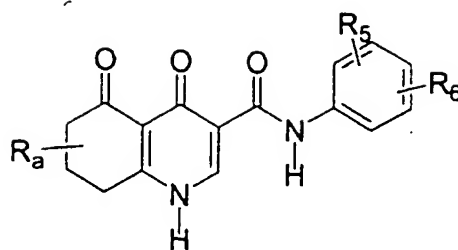
or the pharmaceutically acceptable non-toxic salts thereof wherein:

- 20 R<sub>5</sub> and R<sub>6</sub> are the same or different and represent hydrogen, halogen, hydroxy, lower alkyl, lower alkoxy, amino, mono or dialkylamino where each alkyl portion is lower alkyl, or methylaminoalkyl where each alkyl portion is lower alkyl.

25

5. A compound according to claim 1 of the formula:



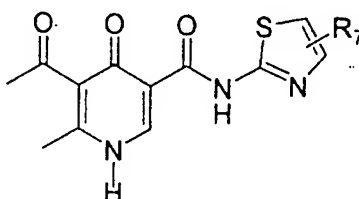


or the pharmaceutically acceptable non-toxic salts thereof wherein:

R<sub>a</sub> is hydrogen, halogen, hydroxy, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkoxy, amino, mono- or di(C<sub>1</sub>-C<sub>6</sub>)alkylamino, or trifluoromethyl;

R<sub>5</sub> and R<sub>6</sub> are the same or different and represent hydrogen, halogen, hydroxy, lower alkyl, lower alkoxy, amino, mono or dialkylamino where each alkyl portion is lower alkyl, or methylaminoalkyl where each alkyl portion is lower alkyl.

6. A compound according to claim 1 of the formula:

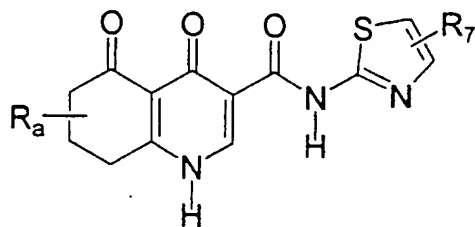


or the pharmaceutically acceptable non-toxic salts thereof

wherein:

R<sub>7</sub> is hydrogen, halogen, hydroxy, lower alkyl, lower alkoxy, amino, mono or dialkylamino where each alkyl portion is lower alkyl, or methylaminoalkyl where each alkyl portion is lower alkyl.

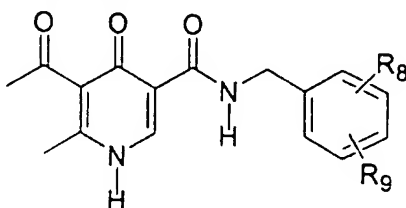
7. A compound according to claim 1 of the formula:



or the pharmaceutically acceptable non-toxic salts thereof  
wherein:

R7 is hydrogen, halogen, hydroxy, lower alkyl, lower alkoxy,  
amino, mono or dialkylamino where each alkyl portion is  
lower alkyl, or methylaminoalkyl where each alkyl portion  
is lower alkyl.

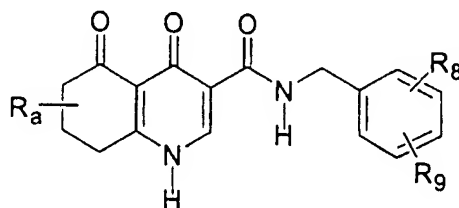
8. A compound according to claim 1 of the formula:



or the pharmaceutically acceptable non-toxic salts thereof  
wherein:

R8 and R9 are the same or different and represent hydrogen,  
halogen, cyano, hydroxy, lower alkyl, lower alkoxy,  
amino, mono or dialkylamino where each alkyl portion is  
lower alkyl, methylaminoalkyl where each alkyl portion is  
lower alkyl.

9. A compound according to claim 1 of the formula:



or the pharmaceutically acceptable non-toxic salts thereof  
wherein:

R8 and R9 are the same or different and represent hydrogen,  
halogen, cyano, hydroxy, lower alkyl, lower alkoxy,  
amino, mono or dialkylamino where each alkyl portion is

lower alkyl, methylaminoalkyl where each alkyl portion is lower alkyl.

10. A compound according to claim 1 which is N-(2-fluorophenyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide.

11. A compound according to claim 1 which is N-(4-methoxyphenyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide.

12. A compound according to claim 1 which is N-(4-methoxy-2-pyridyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide.

13. A compound according to claim 1 which is N-(4-( $\pm$ )-(1-methylaminoethyl)benzyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide.

14. A compound according to claim 1 which is N-(n-Butyl)-1,4,5,6,7,8-hexahydroquinoline-4,5-dione-nicotinic-3-carboxamide.

15. A compound according to claim 1 which is N-(4-ethoxyphenyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide.

16. A compound according to claim 1 which is N-(3-fluorophenyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide.

17. A compound according to claim 1 which is N-(2-fluoro-4-methoxyphenyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide.

18. A compound according to claim 1, which is: N-(3-tolyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide.

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19. A compound according to claim 1 which is N-(2,4-difluorophenyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide.

10

20. A compound according to claim 1 which is N-(2,6-difluorophenyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide.

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21. A compound according to claim 1 which is N-(benzyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide.

22. A compound according to claim 1 which is N-(2-methoxyphenyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide.

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23. A compound according to claim 1 which is N-(3-methylaminomethylphenyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide.

25

24. A compound according to claim 1 which is N-(2-fluorobenzyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide.

30

25. A compound according to claim 1 which is N-(2,3-difluorobenzyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide.

26. A compound according to claim 1 which is N-(isoamyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide.

5        27. A compound according to claim 1 which is N-(4-chlorobenzyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide.

28. A compound according to claim 1 which is N-(phenyl)-  
10 1,4,5,6,7,8-hexahydroquinoline-4,5-dione-nicotinic-3-carboxamide.

29. A compound according to claim 1 which is N-(2-fluorophenyl)-1,4,5,6,7,8-hexahydroquinoline-4,5-dione-  
15 nicotinic-3-carboxamide.

30. A compound according to claim 1 which is N-(2-thiazolyl)-1,4,5,6,7,8-hexahydroquinoline-4,5-dione-nicotinic-  
20 3-carboxamide.

31. A compound according to claim 1 which is N-(benzyl)-1,4,5,6,7,8-hexahydroquinoline-4,5-dione-nicotinic-3-carboxamide.

25        32. A compound according to claim 1 which is N-(2-fluorobenzyl)-1,4,5,6,7,8-hexahydroquinoline-4,5-dione-nicotinic-3-carboxamide.

33. A compound according to claim 1 which is N-(4-methoxybenzyl)-1,4,5,6,7,8-hexahydroquinoline-4,5-dione-  
30 nicotinic-3-carboxamide.

34. A compound according to claim 1 which is N-(phenyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide.

35. A compound according to claim 1 which is N-(Butyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide.

5        36. A compound according to claim 1 which is N-(2(4-Methylthiazoleyl))-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide.

10       37. A compound according to claim 1 which is N-(2-(4-methoxy)pyridyl)-1,4,5,6,7,8-hexahydroquinoline-4,5-dione-nicotinic-3-carboxamide.

15       38. A compound according to claim 1 which is N-(2-thiazolyl)-1,4,5,6,7,8-hexahydroquinoline-4,5-dione-nicotinic-3-carboxamide.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/04303

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D213/82 C07D215/54 C07D417/12 A61K31/455

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 34870 A (NEUROGEN CORPORATION) 25 September 1997 (1997-09-25) the whole document ---	1
A	WO 97 26243 A (NEUROGEN CORPORATION) 24 July 1997 (1997-07-24) the whole document ---	1
A	WO 97 35539 A (THE DUPONT MERCK PHARMACEUTICAL COMPANY) 2 October 1997 (1997-10-02) the whole document -----	

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

27 July 1999

Date of mailing of the international search report

03/08/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Kyriakakou, G

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Initial Application No

PCT/US 99/04303

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